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Spatial variation in T1 of healthy human articular cartilage of the knee joint

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Abstract: The longitudinal relaxation time T(1) of native cartilage is frequently assumed to be constant. To redress this, the spatial variation of T(1) in unenhanced healthy human knee cartilage in different compartments and cartilage layers was investigated. Knees of 25 volunteers were examined on a 1.5 T MRI system. A three-dimensional gradient-echo sequence with a variable flip angle, in combination with parallel imaging, was used for rapid T(1) mapping of the whole knee. Regions of interest (ROIs) were defined in five different cartilage segments (medial and lateral femoral cartilage, medial and lateral tibial cartilage and patellar cartilage). Pooled histograms and averaged profiles across the cartilage thickness were generated. The mean values were compared for global variance using the Kruskal-Wallis test and pairwise using the Mann-Whitney U-test. Mean T(1) decreased from 900-1100 ms in superficial cartilage to 400-500 ms in deep cartilage. The averaged T(1) value of the medial femoral cartilage was 702 \pm 68 ms, of the lateral femoral cartilage 630 \pm 75 ms, of the medial tibial cartilage 700 \pm 87 ms, of the lateral tibial cartilage 594 \pm 74 ms and of the patellar cartilage 666 \pm 78 ms. There were significant differences between the medial and lateral compartment ($p < 0.01$). In each cartilage segment, T(1) decreased considerably from superficial to deep cartilage. Only small variations of T(1) between different cartilage segments were found but with a significant difference between the medial and lateral compartments.

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Spatial variation in T_1 of healthy human articular cartilage of the knee joint

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ABSTRACT. The longitudinal relaxation time T_1 of native cartilage is frequently assumed to be constant. To redress this, the spatial variation of T_1 in unenhanced healthy human knee cartilage in different compartments and cartilage layers was investigated. Knees of 25 volunteers were examined on a 1.5T MRI system. A three-dimensional gradient-echo sequence with a variable flip angle, in combination with parallel imaging, was used for rapid T_1 mapping of the whole knee. Regions of interest (ROIs) were defined in five different cartilage segments (medial and lateral femoral cartilage, medial and lateral tibial cartilage and patellar cartilage). Pooled histograms and averaged profiles across the cartilage thickness were generated. The mean values were compared for global variance using the Kruskal–Wallis test and pairwise using the Mann–Whitney U -test. Mean T_1 decreased from 900–1100 ms in superficial cartilage to 400–500 ms in deep cartilage. The averaged T_1 value of the medial femoral cartilage was 702 ± 68 ms, of the lateral femoral cartilage 630 ± 75 ms, of the medial tibial cartilage 700 ± 87 ms, of the lateral tibial cartilage 594 ± 74 ms and of the patellar cartilage 666 ± 78 ms. There were significant differences between the medial and lateral compartment ($p < 0.01$). In each cartilage segment, T_1 decreased considerably from superficial to deep cartilage. Only small variations of T_1 between different cartilage segments were found but with a significant difference between the medial and lateral compartments.

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MRI relaxation parameters are used to evaluate cartilage degradation. T_2 has been investigated extensively and has been demonstrated to vary with water and collagen content and with collagen orientation in the different cartilage layers [1–8].

The quantification of the longitudinal relaxation time T_1 of native cartilage has received less attention. In experimental studies, native T_1 has been demonstrated to correlate with mechanical properties [9] and to depend upon the macromolecular structure of cartilage [10]. However, it is frequently assumed to be constant across cartilage [11–13]. A few studies have investigated the mean values of a single compartment (Table 1) [10, 14–19] but have not investigated the depth-dependent variation. To our knowledge, no study has systematically compared T_1 of unenhanced human knee cartilage in different cartilage layers and in different cartilage compartments in healthy volunteers.

Usually, inversion-recovery (IR) sequences have been used to measure several points in the T_1 relaxation curve. Although this technique provides ideal measurements of T_1 , it is not viable in most studies that require T_1 values of a large volume within a reasonable time. Three-dimensional (3D) T_1 mapping techniques were applied for this purpose [17, 20–22].

The purpose of this study was to investigate the spatial variation of native cartilage T_1 in different compartments and different cartilage layers in healthy human knee

joints using a rapid 3D gradient-echo (GE) sequence with variable flip angle.

Methods and materials

Volunteers

25 volunteers (15 women, 10 men) with a mean age of 31.2 years (range, 18–42 years) were recruited for MRI. Their mean body mass index was 24.3 (range, 19–26).

After the MRI protocol was explained to them, all of the participants consented to participate in the study, which was approved by our institutional review board. Inclusion criteria were young volunteers practising not more than 3 h of sporting activities per week, a normal body mass index, no history of knee surgery or knee injury, no current joint pain, swelling or morning stiffness, and normal-appearing cartilage on MRI.

The right knee was imaged in each subject. Five subjects were imaged a second time within 10 days in order to test the reproducibility after repositioning; three volunteers were imaged with a two-dimensional (2D) IR turbo spin-echo sequence (IR-TSE) to verify the accuracy of the T_1 values *in vivo*.

MRI

All imaging was performed with a 1.5T system (Magnetom Espree; Siemens Medical Solutions,

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Table 1. *T₁* of healthy human articular cartilage in the knee joint

	Sequence	<i>T₁</i> (ms)				
	Field strength	Lateral femoral	Medial femoral	Lateral tibial	Medial tibial	Patellar
Van Breuseghem et al [16]	Combined <i>T₁</i> – <i>T₂</i> IR-TSE 1.5 T	449 ± 34*				–
Tiderius et al [18]	Turbo-IR 1.5 T	952 ± 86	952 ± 86	–	–	–
Williams et al [14]	Turbo-IR 1.5 T 3.0 T	–	916 ± 102 1146 ± 133	–	819 ± 86 1167 ± 79	–
Gold et al [19]	Look-Locker 1.5 T 3.0 T	–	–	–	–	1066 ± 155 1240 ± 107
Wang et al [15]	3D GE with VFA 3.0 T	1004 ± 72*				1193 ± 108
Trattinig et al [17]	3D GE with VFA 3.0 T	1013 ± 89	–	–	–	–

Data are presented as the mean ± standard deviation. VFA, variable flip angle; GE, gradient echo; IR, inversion-recovery; IR-TSE, inversion-recovery turbo spin-echo; 3D, three-dimensional.

*Mean value averaged over the femorotibial compartment.

Erlangen, Germany) using an eight-channel knee coil. For the evaluation of the cartilage sagittal *T₂* weighted 3D water excitation, true fast imaging with steady-state precession (TrueFISP) images were acquired. The sequence parameters were repetition time, 12.4 ms; echo time, 5.3 ms; flip angle, 28°; section thickness, 1.7 mm; field of view, 18 × 18 cm; and matrix, 512 × 512.

For *T₁* mapping of the entire knee joint, a dual flip-angle 3D GE sequence in combination with parallel imaging (acceleration factor =2) was performed in the

sagittal plane [15, 17]. The sequence parameters were repetition time, 13.2 ms; echo time, 5.4 ms; flip angle, 4.7° and 26.2°; effective section thickness, 3 mm; number of excitations, 3; field of view, 12 × 12 cm; and matrix, 256 × 256. The 2 optimum flip angles were selected as those with signals that were 71% of the Ernst angle signal [15, 23], which is the greatest signal for a given repetition time and *T₁*. The acquisition time was 5.05 min.

The accuracy of the *T₁* values obtained with the dual flip-angle 3D GE sequence was evaluated using

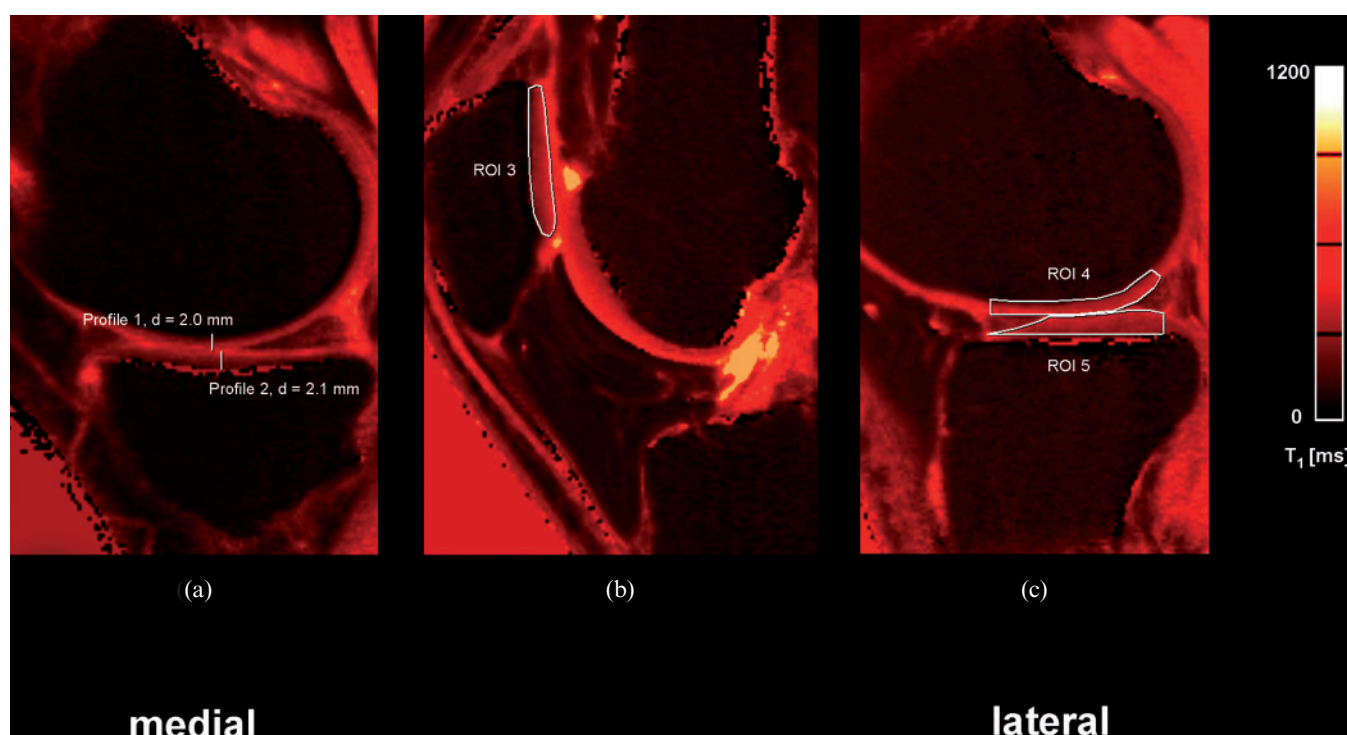


Figure 1. Colour-coded mid-sagittal *T₁* maps through (a) the medial femorotibial joint, (b) the femoropatellar joint and (c) the lateral femorotibial joint. *T₁* maps of the whole knee joint were acquired with a dual flip-angle three-dimensional gradient-echo sequence in 5.05 min. Profiles perpendicular to the cartilage surface (a) and regions of interest in the weight-bearing areas of different cartilage segments (b,c) were annotated.

phantoms with a range of T_1 values similar to those observed in articular cartilage (500–1100 ms) (Table 1) and *in vivo* in three volunteers.

Phantoms were prepared by diluting 2 mmol l⁻¹ gadopentetate dimeglumine solution (Magnevist®; Bayer Schering AG, Berlin, Germany) with distilled water. A 2D IR-TSE sequence was used with five inversion times (TIs) ranging from 50 to 2500 ms to

calculate T_1 values of the phantoms, and with seven inversion times ranging from 50 to 1700 ms to calculate T_1 values of the knee cartilage. The sequence parameters were repetition time, 3000 ms; echo time, 13 ms; section thickness, 3 mm; field of view, 12 × 12 cm; and matrix, 256 × 256. The acquisition time was 21 min. The T_1 values obtained with the 2D IR-TSE sequence were considered as reference values.

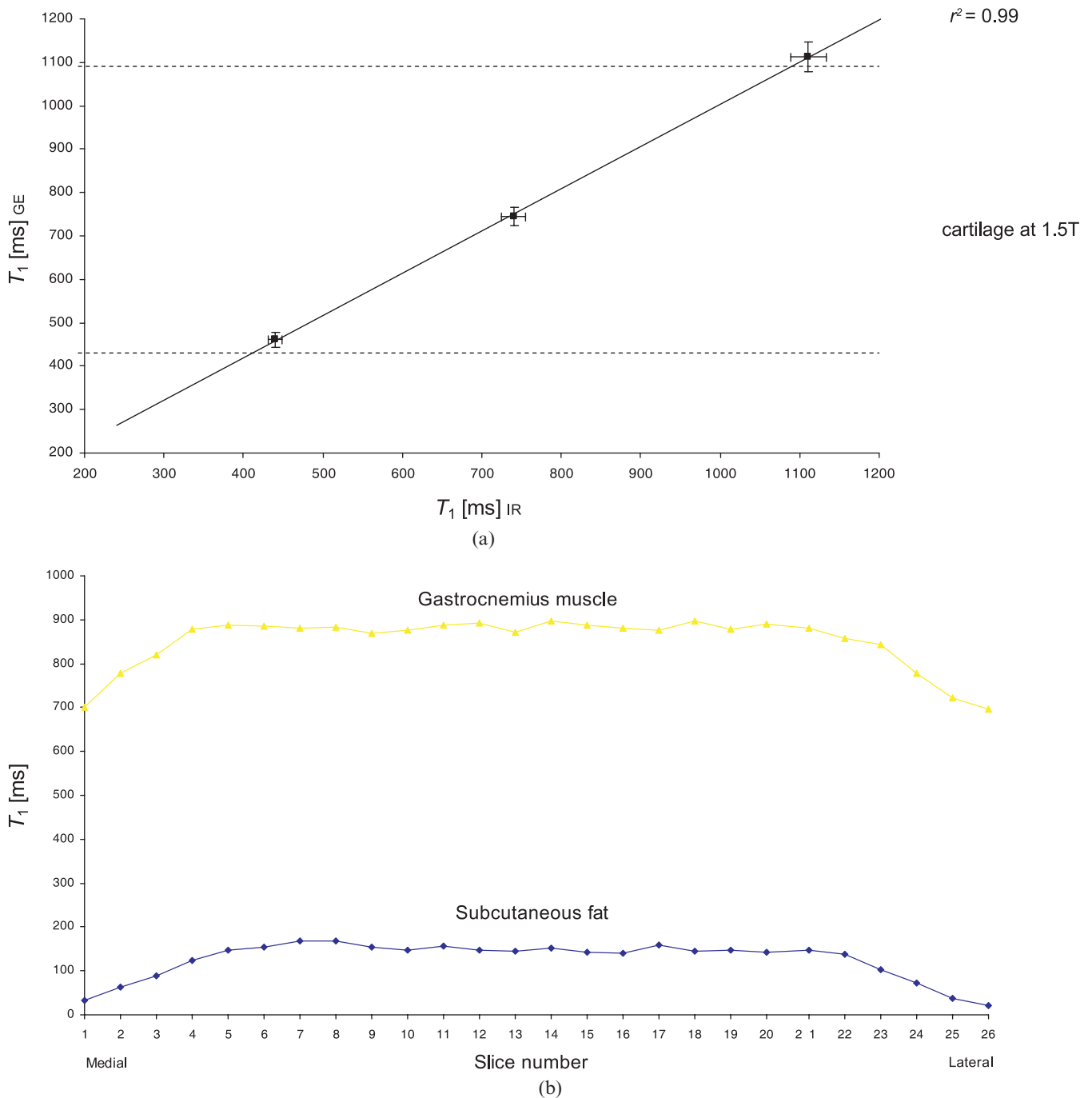


Figure 2. (a) Comparison of T_1 values from the dual flip-angle three-dimensional gradient echo (3D GE) and the two-dimensional inversion-recovery turbo spin-echo sequence (2D IR-TSE) obtained from phantom measurements. (b) Profile plots of the T_1 variation along a horizontal line from the medial to the lateral compartment are demonstrated. Systematically lower T_1 values were measured in the outer sections in the periphery of the coil. (c) Comparison of T_1 values of the femoral, tibial and patellar cartilage obtained with 3D GE and the 2D IR-TSE sequences *in vivo*. (d) The Bland–Altman plot demonstrates no bias and good agreement between the two techniques. Horizontal lines are drawn at the mean difference and ± 1.96 times the standard deviation.

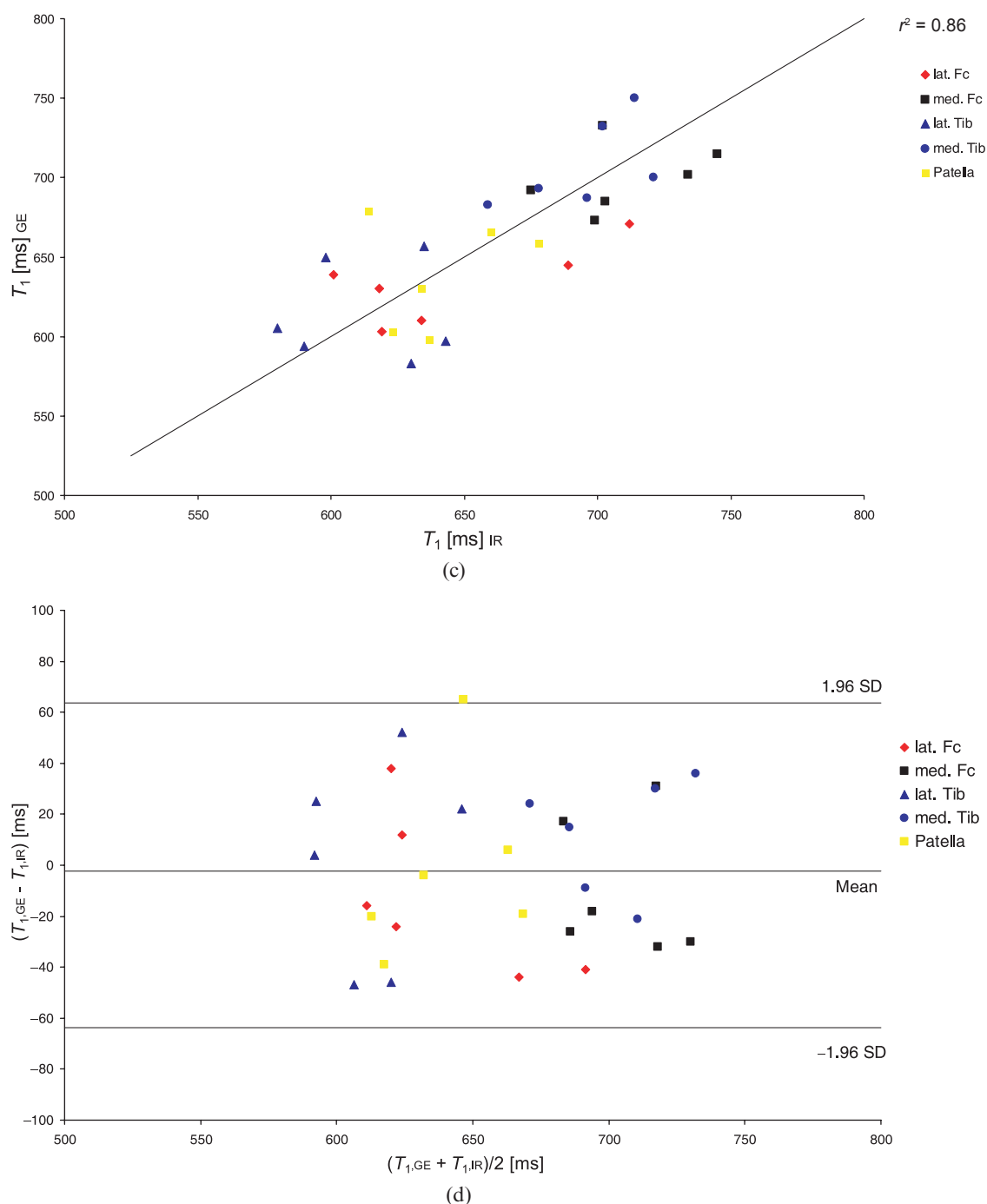


Figure 2. (continued)

Data analysis

The high-resolution TrueFISP images were evaluated to exclude areas with cartilage defects or thinning. Sagittal T_1 parameter images were calculated using the proprietary software of the parameter mapping package of the MRI console.

For the quantification of T_1 relaxation times, 2 adjacent sagittal T_1 images were selected for each of the following positions: centre of the medial and lateral femorotibial compartment (4 images), and the centre of the patella (2 images) in each of the 25 knee joints.

Polygonal regions of interest (ROIs) of about 450–750 pixels were drawn in the weight-bearing area of the femoral and tibial cartilage (Figure 1) of both the medial and lateral compartments (two ROIs per image) and in the patellar cartilage (one ROI per image). A total of 250 ROIs were drawn manually by a single investigator.

Reproducibility

In five volunteers, two MR data sets were acquired within 10 days. Intrasubject reproducibility of the mean T_1 values of each cartilage segment was calculated as the

Table 2. Coefficient of variation (CoV) for T_1 of knee cartilage calculated by the formula $100 \times (\text{standard deviation/average})$

$n = 5$	Lateral femoral	Medial femoral	Lateral tibial	Medial tibial	Patellar
CoV (%)	5.7	5.3	5.6	5.1	5.9

Data were acquired in five healthy knee joints with an interval of 10 days.

Table 3. T_1 of healthy human articular cartilage in weight-bearing areas of the knee joint at 1.5 T ($n = 25$)

	T_1 (ms)				
	Lateral femoral	Medial femoral	Lateral tibial	Medial tibial	Patellar
Slice I	630 ± 69 (501–754)	702 ± 68 (617–855)	594 ± 65 (509–726)	700 ± 87 (549–897)	666 ± 78 (519–797)
Slice II	639 ± 65 (563–724)	692 ± 65 (610–812)	605 ± 55 (522–727)	693 ± 62 (612–817)	659 ± 76 (512–771)

Data are presented as the mean \pm standard deviation. Ranges are enclosed in parentheses.

coefficient of variation (CoV) by the formula $100 \times (\text{standard deviation/average})$.

Spatial variation of T_1

To evaluate the spatial variation of cartilage T_1 through the knee joint, mean values and pooled histograms obtained from 250 ROIs of 5 cartilage segments (lateral femoral condyle, medial femoral condyle, lateral tibial plateau, medial tibial plateau and patella) were calculated. In addition, averaged profiles from 25 volunteers were generated in each cartilage segment.

Statistical analysis

The Pearson correlation coefficient between the T_1 values obtained with the 3D GE and with the 2D IR-TSE sequence was calculated. A Bland–Altman plot was used to compare the two measurements techniques. This plots the difference between the two measurements on the y -axis and the average of the two measurements on the x -axis. The distribution-free Kruskal–Wallis test with a post-hoc Mann–Whitney U -test was used for comparison of the T_1 relaxation times between the different cartilage segments. $p < 0.05$ was considered statistically significant. For statistical analyses, SPSS software (SPSS version 11.0; SPSS, Chicago, IL) was used.

Results

T_1 measurements made in a phantom with T_1 values in the range 500–1100 ms using the dual flip-angle 3D GE and the 2D IR-TSE sequences are shown in Figure 2a. Linear regression analysis shows good agreement between the 2D IR-TSE and 3D measurements ($r^2 = 0.99$). Because of field inhomogeneities in the periphery of the coil, systematically lower T_1 values were measured in the outer sections (Figure 2b) [17]. Those outer sections with a difference in T_1 greater than the standard deviation calculated from the 12 mid-sagittal sections were excluded. 8 out of 26 sections were excluded from analysis.

Figure 2c shows the T_1 values for each ROI of the femoral, tibial and patellar cartilage of two sections from the medial, lateral and patellar compartments obtained with 3D GE and 2D IR-TSE sequences from three

volunteers. Linear regression analysis demonstrates good agreement between the 2D IR-TSE and 3D GE measurements ($r^2 = 0.86$). There was no significant difference between the mean T_1 values obtained from both measurements ($p = 0.8$). The Bland–Altman plot (Figure 2d) demonstrates no bias in the T_1 values obtained with the 3D GE and 2D IR-TSE sequences. The mean difference between both measurements was -2.2 ± 31.8 ms and was not significantly different from zero ($p = 0.7$).

Figure 1 provides examples of T_1 maps of sagittal sections through the middle of the medial femorotibial joint, the patella and the lateral femorotibial joint obtained with the dual flip-angle 3D GE sequence. Profiles and ROIs were annotated on the T_1 maps in the weight-bearing areas of the different cartilage segments.

The reproducibility of mean cartilage T_1 in the five cartilage segments was in the range of CoV = 5.1% to CoV = 5.9% (Table 2).

The mean T_1 values of two consecutive sections from the five cartilage segments are summarised in Table 3. The Kruskal–Wallis test demonstrated significant differences ($p < 0.001$) in the mean T_1 between different cartilage segments. There was no significant difference between the mean T_1 values from the same segment of two consecutive sections ($p = 0.2$). Pairwise comparison using the Mann–Whitney U -test revealed significant differences between the mean T_1 of the lateral tibial plateau (594 ± 65 ms) and the medial tibial plateau (700 ± 87 ms) ($p = 0.002$), and between the lateral femoral condyle (630 ± 69 ms) and the medial femoral condyle (702 ± 68 ms) ($p = 0.01$). There was no significant difference between the T_1 values of the lateral femoral condyle and lateral tibial plateaus ($p = 0.1$) and those of the medial femoral condyle and medial tibial plateaus ($p = 0.9$). The pooled histograms obtained from 25 volunteers demonstrate a wide range of cartilage T_1 values, approximately 400–1100 ms, within the ROIs (Figure 3).

To demonstrate the depth-dependent variation of T_1 , averaged profiles perpendicular to the cartilage surface are shown in Figure 4. In each cartilage segment, T_1 decreased going from the superficial to the deep cartilage, with a maximal T_1 of 900–1100 ms near the cartilage surface to a minimum value of 400–500 ms at the cartilage bone interface.

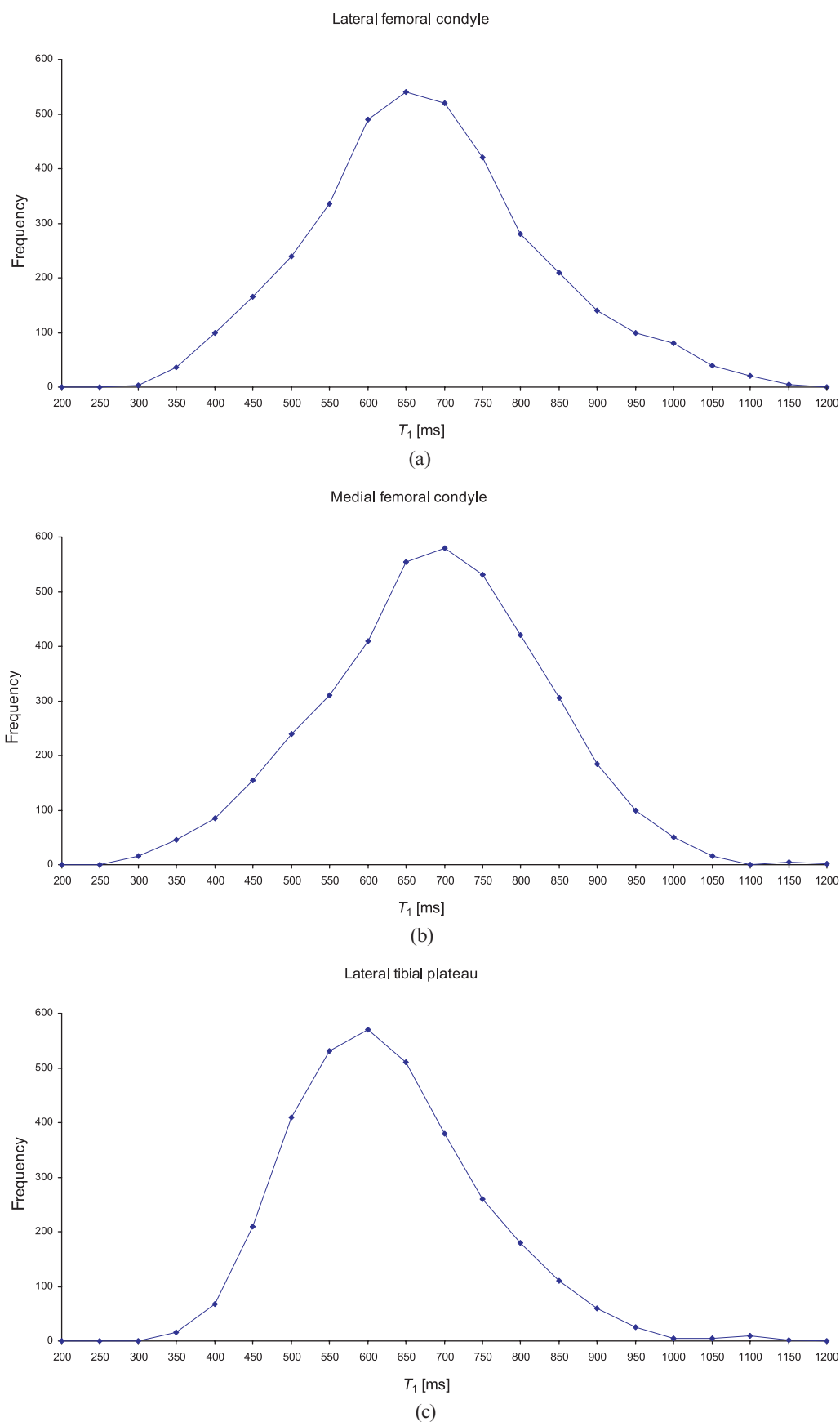


Figure 3. Pooled histograms of T_1 values obtained from 25 volunteers with healthy knee cartilage. Different cartilage segments of the knee joint — (a) lateral femoral condyle, (b) medial femoral condyle, (c) lateral tibial plateau, (d) medial tibial plateau and (e) patellar — were evaluated. A wide range of T_1 values from ~ 400 ms to 1100 ms could be observed in each segment.

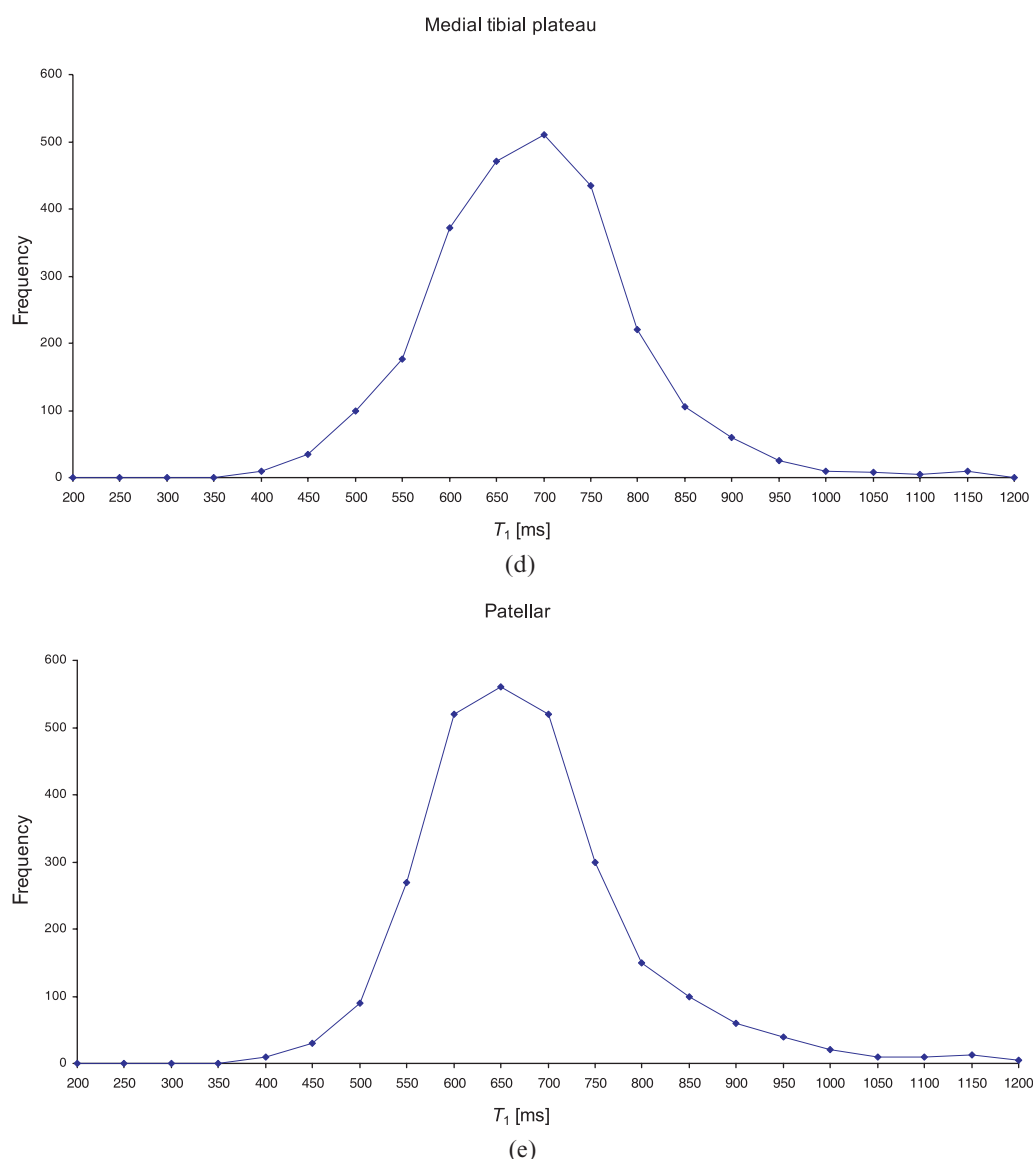


Figure 3. (continued)

Discussion

The presented data demonstrate significant differences in T_1 of unenhanced knee cartilage in different layers and compartments at 1.5 T.

Mean T_1 values of healthy knee cartilage at 1.5 T using the variable flip-angle technique were comparable to the few published studies (mostly using IR techniques) [14, 16, 18], and the reproducibility for rapid T_1 measurements with the variable flip-angle technique was accurate (CoV = 5.1–5.9%).

In our study, T_1 decreased markedly from the superficial to deep cartilage zones in all knee compartments (Figure 4). This finding is consistent with published data obtained from human and bovine cartilage samples *ex vivo*, indicating that T_1 depends on the macromolecular structure of cartilage [10, 24]. This effect is considerably stronger at lower field strengths and could impact the quantification of tissue contrast agent concentrations in human cartilage *in vivo*.

The large range of T_1 values (400–1100 ms) observed in the pooled histograms (Figure 3) obtained from the

different knee compartments is caused by the depth dependence of T_1 . The observed variation in mean cartilage T_1 between different compartments is small, but significant differences between the medial and lateral knee compartments were found (Table 3; Figure 3). This may be explained by differences in cartilage thickness [25, 26] and cartilage load [27] between the medial and lateral compartments. A systematic error seems unlikely because the 18 sections used for the evaluation provide constant T_1 values in the subcutaneous fat and gastrocnemius muscle (Figure 2b).

The 3D GE sequence with variable flip angle can be used for rapid and accurate T_1 mapping with high resolution and volume coverage. As demonstrated, the phantom and *in vivo* T_1 values show good agreement with the standard 2D IR method (Figure 2). B_1 inhomogeneity is the main source of errors that could require the correction of T_1 values, especially at higher field strengths.

Inhomogeneities in the spatial distribution of the transmitted field B_1 is the main source of errors.

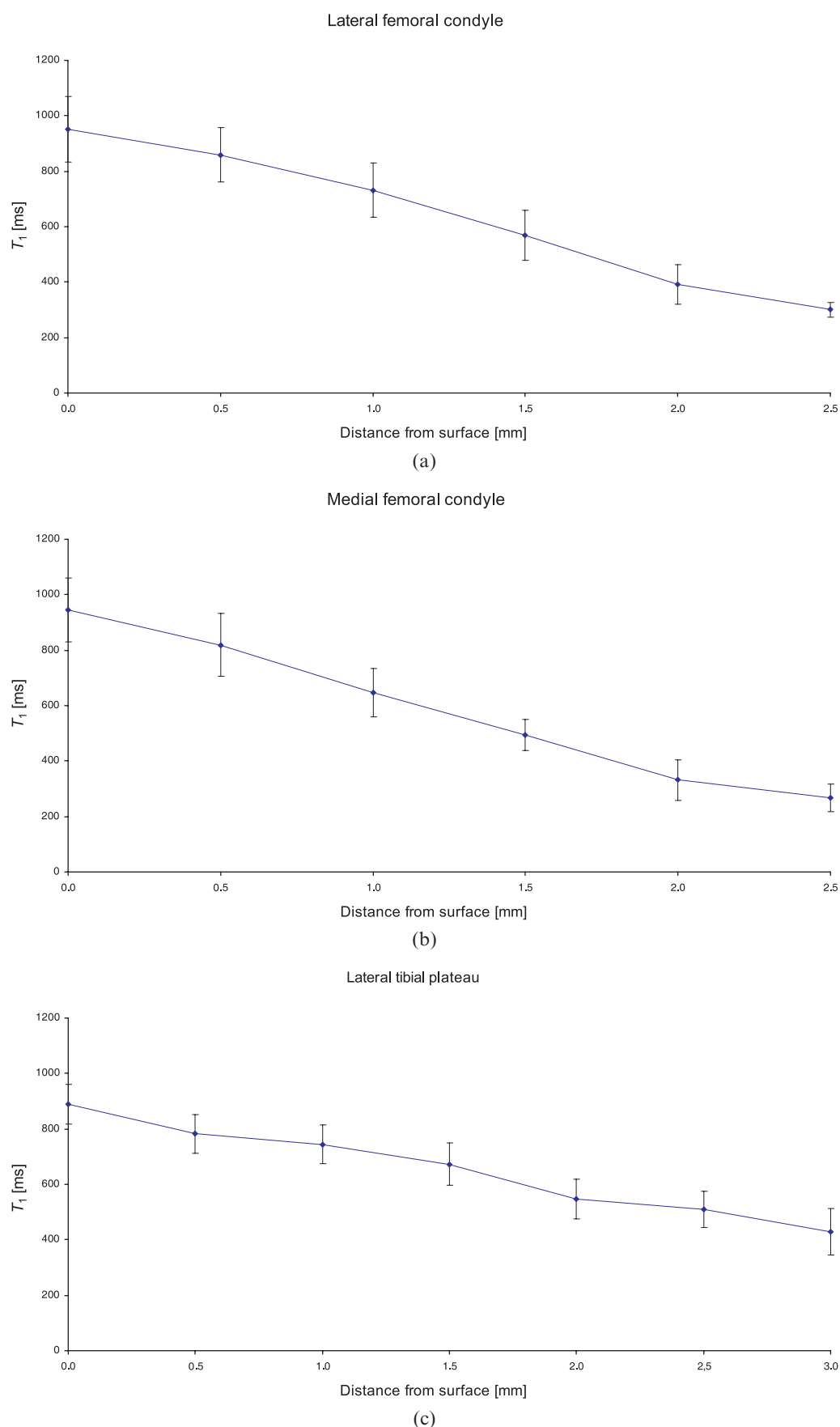


Figure 4. Averaged T_1 profiles from different cartilage segments — (a) lateral femoral condyle, (b) medial femoral condyle, (c) lateral tibial plateau, (d) medial tibial plateau and (e) patella. The data were obtained from 25 knee joints. The standard deviation is marked by vertical lines. Human healthy knee cartilage demonstrates a continuous decrease from superficial to deep cartilage.

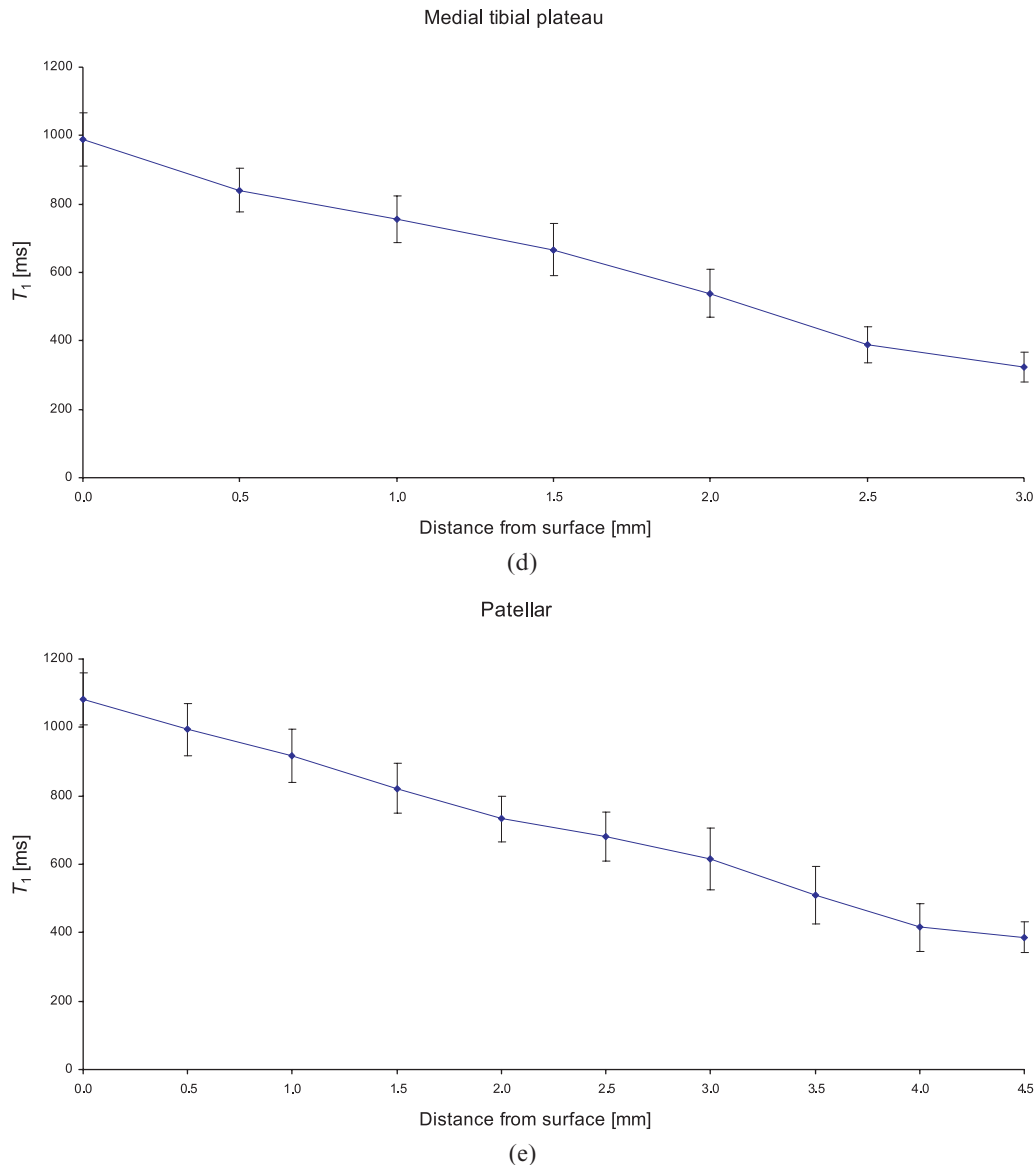


Figure 4. (continued)

However, Wang et al [15] demonstrated that the variations in flip angle are less than 5% within cartilage, even at 3 T. Furthermore, the correlation of T_1 with age, BMI and gender was not evaluated because we investigated a small cohort (young volunteers with healthy cartilage). This issue warrants further research.

In conclusion, T_1 decreased considerably from the superficial to deep cartilage in each compartment at 1.5 T. Only small variations in mean cartilage T_1 between different knee compartments were found, with a small but significant difference between the medial and lateral compartments.

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